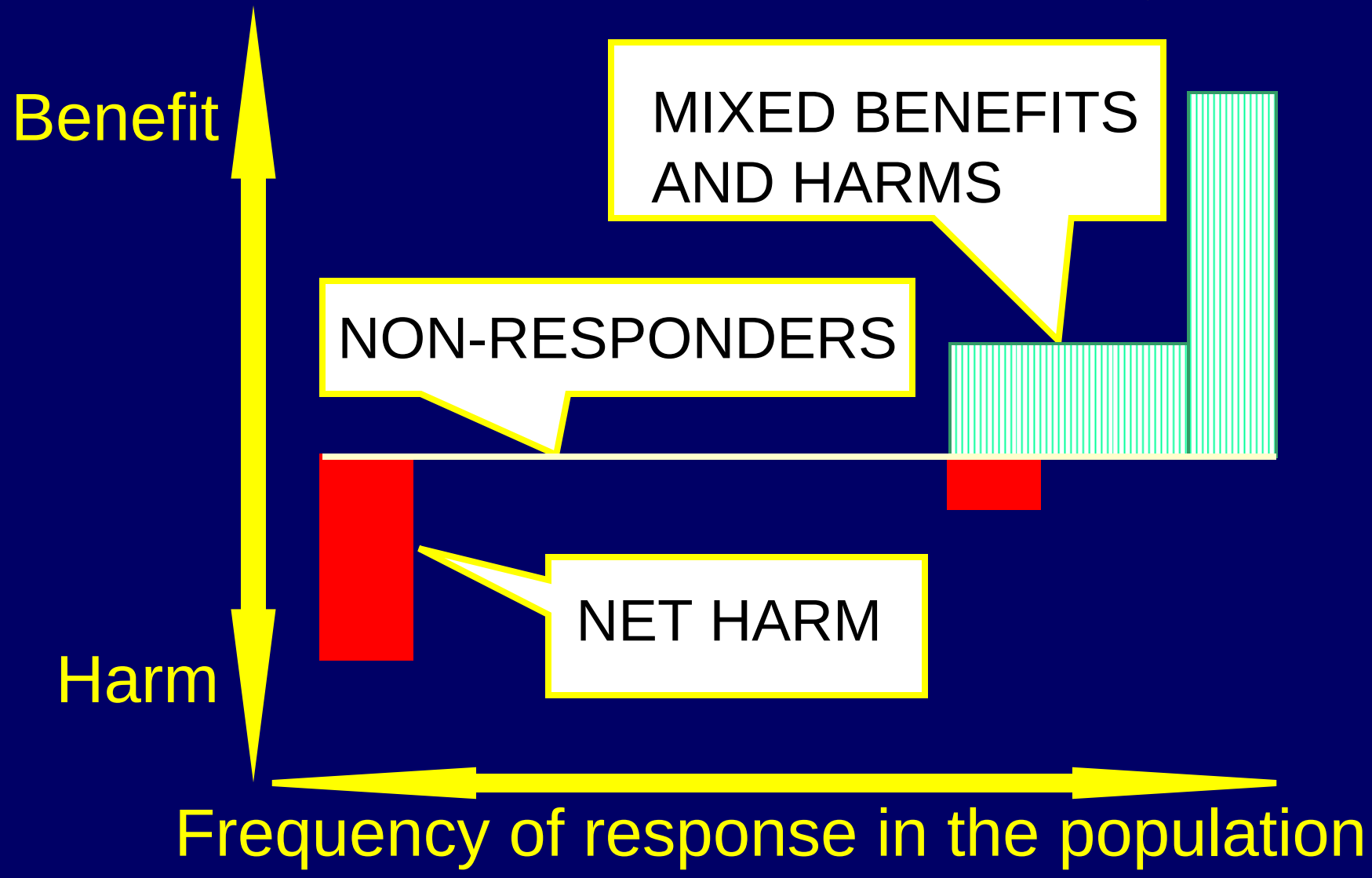
Clinical Pharmacology and Translational Research Symposium:
Translation of Pharmaceutical Science to Practice
FIP Pharmaceutical Sciences World Congress- American Association of Pharmaceutical Scientists Annual meeting, November 16, 2010
New Orleans, LA

# Scientific Perspective on Pharmacogenetic Tests Informing Clinical Decisions

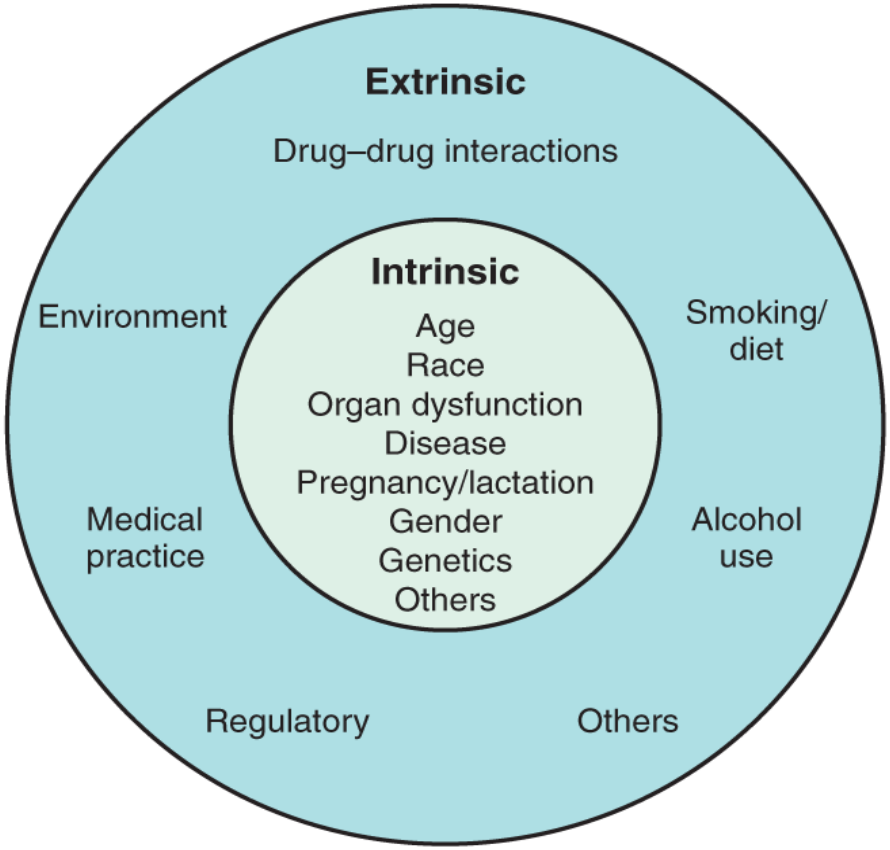
Shiew-Mei Huang, Ph.D.
Deputy Director
Office of Clinical Pharmacology (OCP)
OTS, CDER, FDA
shiewmei.huang@fda.hhs.gov

# Variability of Patient Response




*Barbara Evans, Notre Dame Law Review 85(2);419-524, 2010*
*http://www.nd.edu/~ndlrev/archive_public/85ndlr2/Evans.pdf*

# Many Factors Affect Drug Exposure/Response




It is critical to evaluate how these factors affect drug exposure/response

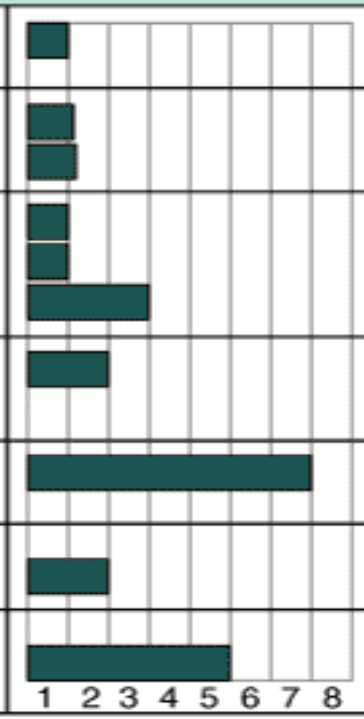
Ultimate goal → Optimal dosing for patients with these individual factors

*Huang S-M, Temple R, Is this the Drug or Dose for you? Clin Pharmacol Ther 84: 287-294, 2008*

*<FDA Clinical Pharmacology guidance documents: http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm*

# Comparative exposure and dose recommendation in subgroups with various patient factors

| Group | Ethnic factor | Fold change in exposure (AUC) | Initial dose (mg) | Daily dose (mg) |
|---|---|---|---|---|
| 1 | Control | 1-fold | 10–20 | 5–40 |
| 2 | Hepatic impairment | 1.1-fold (mild)<br>1.2-fold (moderate) | 10–20<br>10–20 | 5–40<br>5–40 |
| 3 | Renal impairment | 1-fold (mild)<br>1-fold (moderate)<br>3-fold (severe) | 10–20<br>10–20<br>5 | 5–40<br>5–40<br>≤10 |
| 4 | Race | 2-fold (Asians) | 5 | 5–20 |
| 5 | Cyclosporine | 7-fold | | 5 |
| 6 | Gemfibrozil | 1.9-fold | | 10 |
| 7 | Lopinavir/ ritonavir | 5-fold | | 10 |




(Data compiled from labeling for Crestor (rosuvastatin; AstraZeneca); Labeling from http://www.accessdata.fda.gov/scripts/cder/drugsatfda.); November 2007 labeling

→Current practice: Adjust the dose to achieve similar systemic exposure → Only the first step

*<Huang S-M, Temple R, Clin Pharmacol Ther. 84(3): 287-294, 2008>*

# Risk Communications

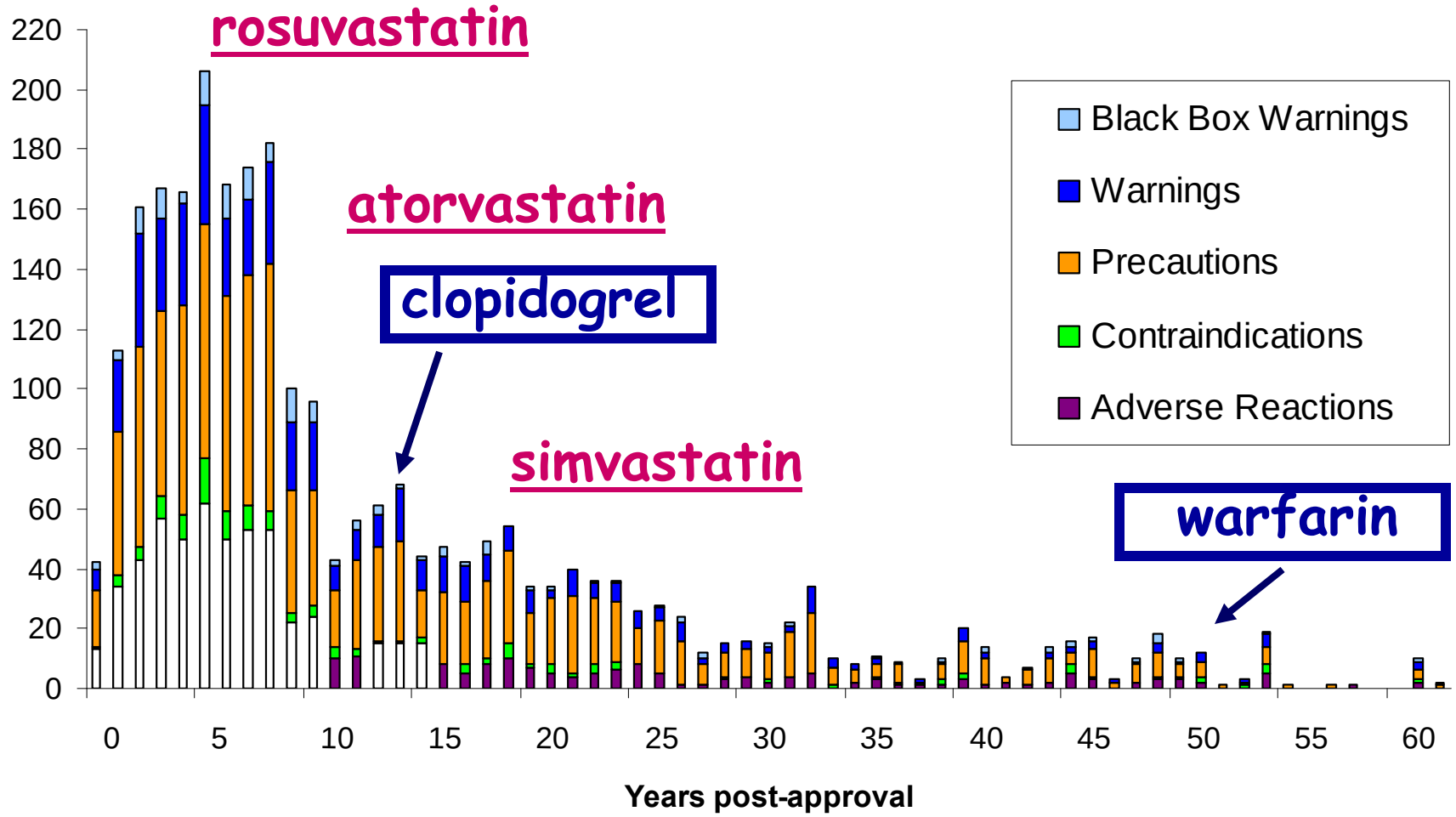
An important facet of FDA's risk communication strategy and mission has always been educating the public about the appropriate use of FDA-regulated products.

"….education involves more than ensuring the accuracy of product labeling …"

*FDA Strategic Plan for Risk Communications, September 30, 2009*
*http://www.fda.gov/AboutFDA/ReportsManualsForms/Reports/ucm183673.htm*

# Composition of Safety-Related Labeling Changes for All Drug Products

**(changes made Oct 2002-Aug 2005, n=2645 label changes for 1601 NDA/BLA entries)**

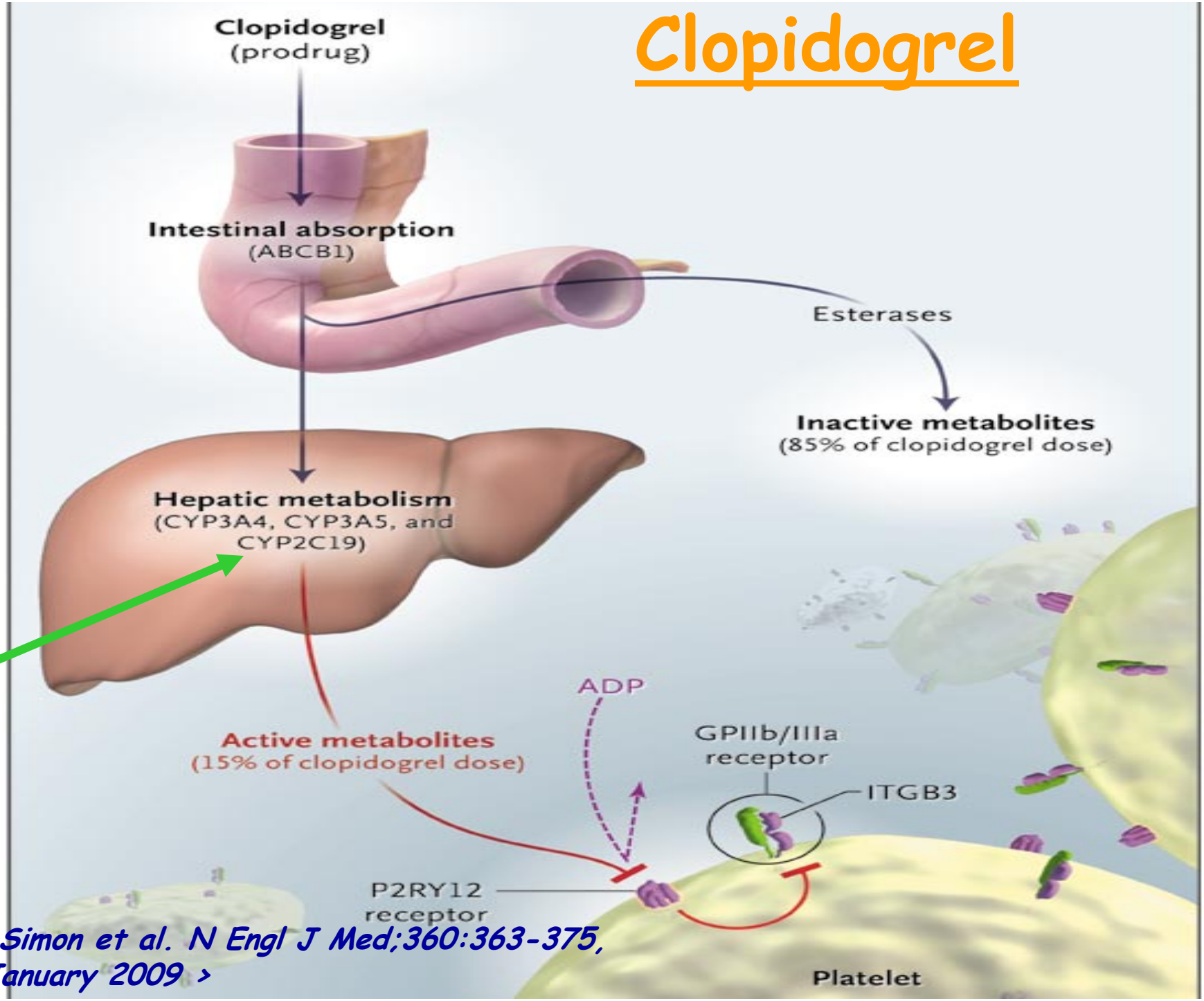



*Modified from: T Mullin, CDER, Office of Planning and Analysis, OTS presentation, May 2009*

# Labeling Example (1)

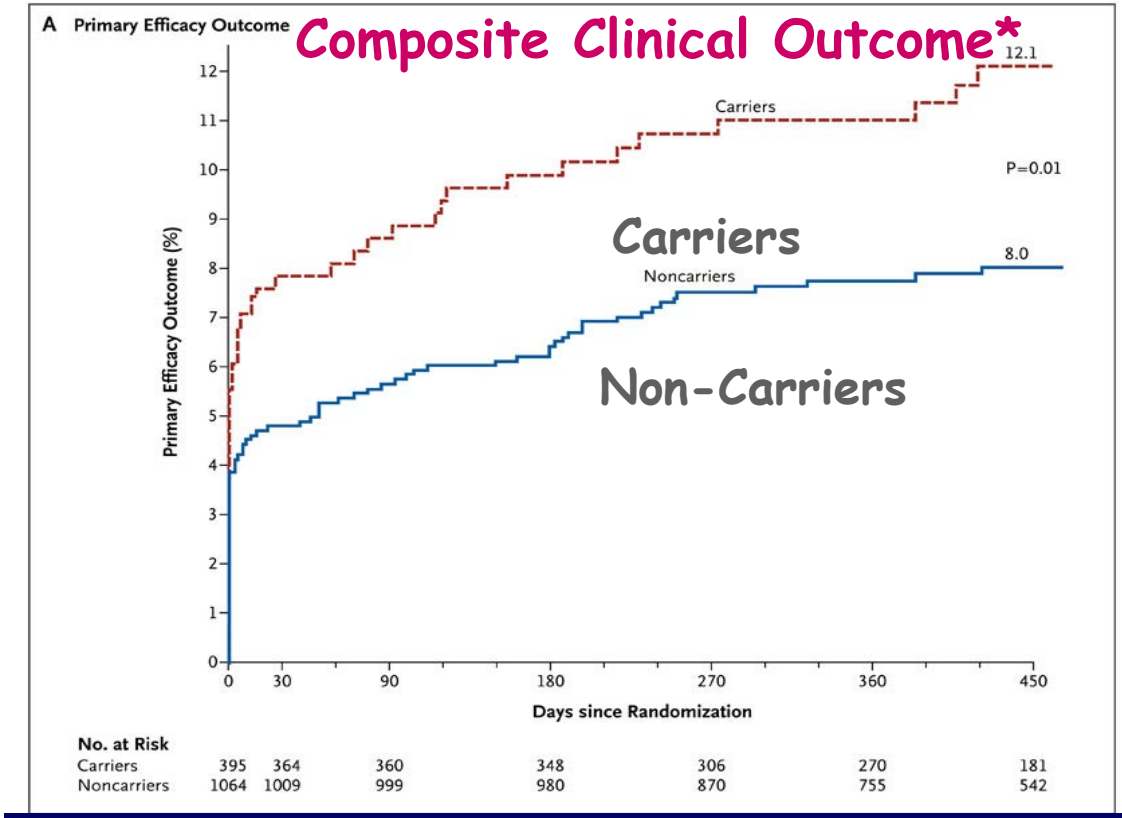
Updating labeling
Genetic Data←→
Drug Interaction warning

# Clopidogrel

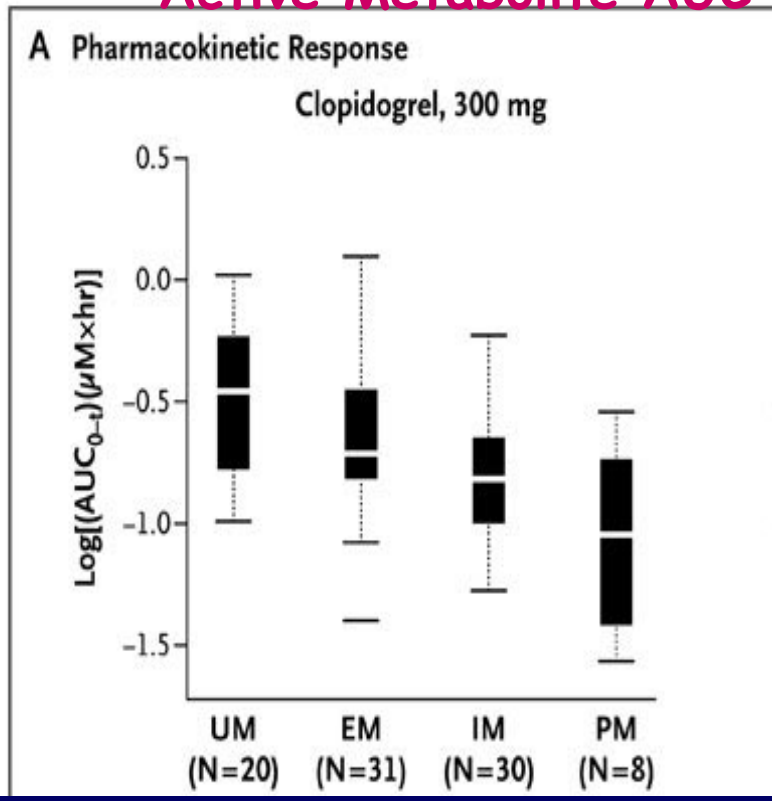



*‹Simon et al. N Engl J Med;360:363-375, January 2009 ›*

# CYP2C19 and Clopidogrel




Active Metabolite AUC




**Carriers:** with at least one variant alleles, *2, 3, 4, 5, 8 (IM+PM);

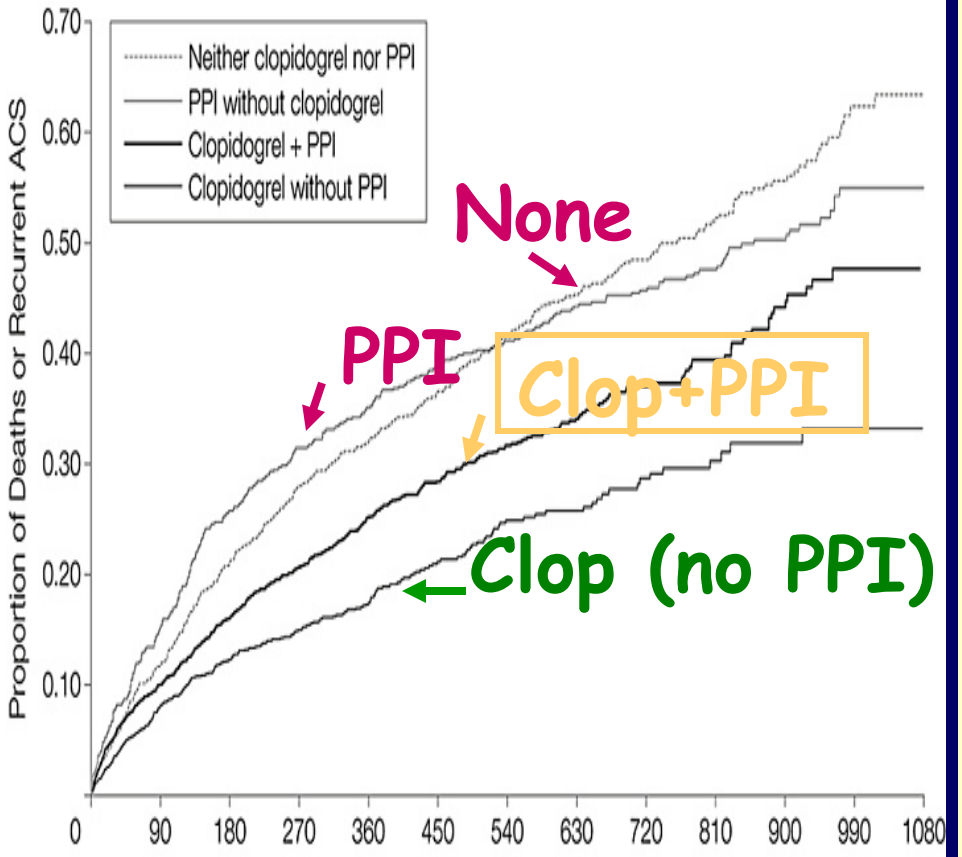
***Outcome:** a composite of death from cardiovascular causes, myocardial infarction, or stroke

**PM:** with two reduced function alleles
**IM:** one reduced function allele
**EM:** no variant alleles;
**UM:** one or two *17

*‹Mega J et al. N Engl J Med 2008;10.1056/NEJMoa0809171 ›*

Another study also examined MDR1

*‹Simon T et al. N Engl J Med 2008; http://content.nejm.org/cgi/content/full/360/4/363*




No. at risk

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| Neither clopidogrel nor PPI | 1223 | 1688 | 1531 | 1127 | 751 | 391 | 180 |
| PPI without clopidogrel | 1093 | 1223 | 1210 | 921 | 585 | 310 | 155 |
| Clopidogrel without PPI | 2425 | 1878 | 1179 | 620 | 362 | 147 | 78 |
| Clopidogrel + PPI | 3931 | 2490 | 1577 | 891 | 494 | 214 | 102 |

*Ho PM, et al, JAMA, March 4, 2009; 301: 937 - 944.*

Medco study (16,690 patients) taking clopidogrel after stenting-- the risk of major adverse cardiovascular events increased to 25% (from 18%) in patients taking PPIs ---

*http://cardiobrief.org/2009/05/06/scai-clopidogrelppi-wed-1130am/; May 6, 2009*

# FDA Actions

## January 2009:Early communication

Healthcare providers should re-evaluate the need for starting or continuing treatment with a PPI, including Prilosec OTC, in patients taking clopidogrel……

*January 26, 2009*
*http://www.fda.gov/cder/drug/early_comm/clopidogrel_bisulfate.htm*

## May 2009: Labeling changes

CYP2C19 poor metabolizer status is associated with diminished response to clopidogrel. The optimal dose regimen for poor metabolizers has yet to be determined

*Drugs at the FDA (Plavix, "DOSAGE and ADMINSTRATION-Pharmacogenetics", & "PRECAUTIONS- Drug Interactions)*
*http://www.accessdata.fda.gov/drugsatfda_docs/label/2009/020839s040lbl.pdf*
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

MedWatch The FDA Safety Information and Adverse Event Reporting Program

Safety Information

Safety Alerts for Human Medical Products

2009 Safety Alerts for Human Medical Products

2008 Safety Alerts for Human Medical Products

2007 Safety Alerts for Human Medical Products

2006 Safety Alerts for Human Medical Products

2005 Safety Alerts for Human Medical Products

2004 Safety Alerts for Human Medical Products

2003 Safety Alerts for Human Medical Products

2002 Safety Alerts for Human Medical Products

2001 Safety Alerts for Human Medical Products

# Clopidogrel (marketed as Plavix) and Omeprazole (marketed as Prilosec) - Drug Interaction

**Audience**: Cardiovascular healthcare professionals, pharmacists

[Posted 11/17/2009] FDA notified healthcare professionals of new safety information concerning an interaction between clopidogrel (Plavix), an anti-clotting medication, and omeprazole (Prilosec/Prilosec OTC), a proton pump inhibitor (PPI) used to reduce stomach acid. New data show that when clopidogrel and omeprazole are taken together, the effectiveness of clopidogrel is reduced. Patients at risk for heart attacks or strokes who use clopidogrel to prevent blood clots will not get the full effect of this medicine if they are also taking omeprazole. Separating the dose of clopidogrel and omeprazole in time will not reduce this drug interaction.

Other drugs that are expected to have a similar effect and should be avoided in combination with clopidogrel include: cimetidine, fluconazole, ketoconazole, voriconazole, etravirine, felbamate, fluoxetine, fluvoxamine, and ticlopidine.

Recommendations for healthcare professionals are provided in the "Information for Healthcare Professionals" sheet.

[11/17/2009 - Information for Healthcare Professionals - FDA]
[11/17/2009 - Public Health Advisory - FDA]
[11/17/2009 - Follow-Up to January 2009 Early Communication - FDA]

Previous MedWatch Alert:

[01/26/2009] Clopidogrel bisulfate (marketed as Plavix) Early Communication

# March 2010 Relabeling

## WARNING: DIMINISHED EFFECTIVENESS IN POOR METABOLIZERS

- Effectiveness of Plavix depends on activation … by …. CYP2C19
- Poor metabolizers ….. exhibit higher cardiovascular event rates following … acute coronary syndrome (ACS). or … percutaneous coronary intervention (PCI) than patients with normal CYP2C19 function
- Tests are available to identify .. CYP2C19 genotype …
- Consider alternative treatment or treatment strategies in patients identified as CYP2C19 poor metabolizers

## WARNINGS AND PRECAUTIONS

- Avoid concomitant use with drugs that inhibit CYP2C19 (e.g., omeprazole)

*Drugs at the FDA (Plavix, "HIGHLIGHTS")*
*http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s042lbl.pdf*
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

# August 2010 Relabeling

**2.3 CYP2C19 Poor Metabolizers**

CYP2C19 poor metabolizer status is associated with diminished antiplatelet response to clopidogrel. Although a higher dose regimen in poor metabolizers increases antiplatelet response *[see Clinical Pharmacology (12.5)]*, an appropriate dose regimen for this patient population has not been established.

**2.4 Use with Proton Pump Inhibitors (PPI)**

Omeprazole, a moderate CYP2C19 inhibitor, reduces the pharmacological activity of Plavix. Avoid using omeprazole concomitantly or 12 hours apart with Plavix. Consider using another acid-reducing agent with less CYP2C19 inhibitory activity. A higher dose regimen of clopidogrel concomitantly administered with omeprazole increases antiplatelet response; an appropriate dose regimen has not been established *[see Warnings and Precautions (5.1), Drug Interactions (7.1) and Clinical Pharmacology (12.5)]*.

*Drugs at the FDA*
*http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/020839s048lbl.pdf*
**http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/**

# October 2010 Publication

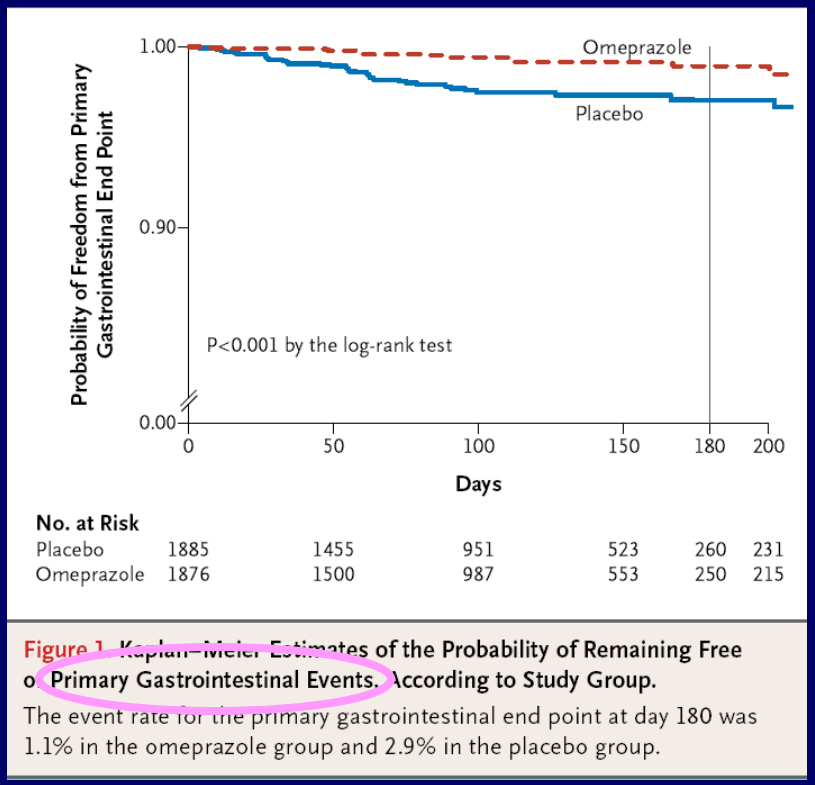



Figure 1. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Gastrointestinal Events, According to Study Group.
The event rate for the primary gastrointestinal end point at day 180 was 1.1% in the omeprazole group and 2.9% in the placebo group.

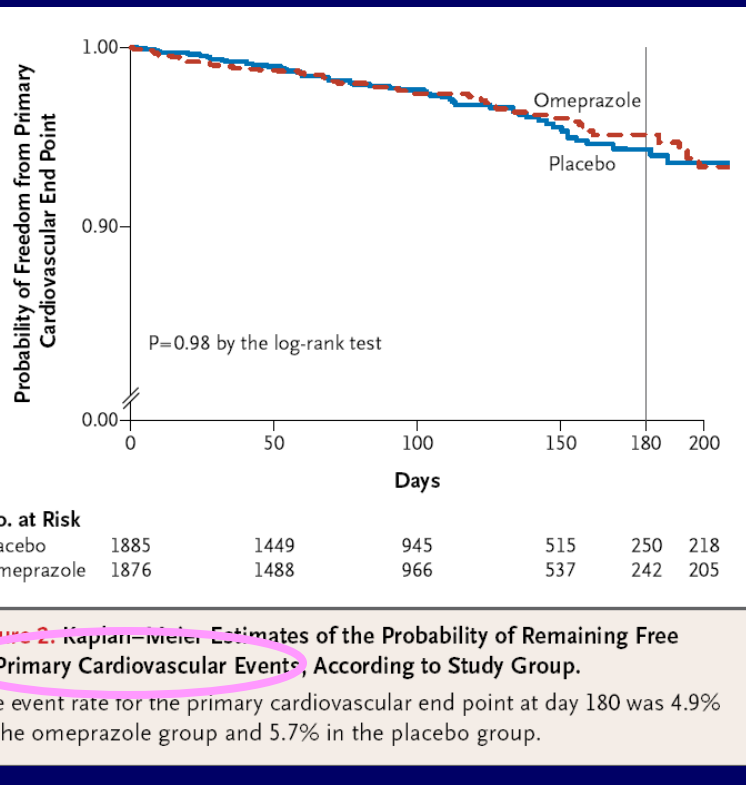



Figure 2. Kaplan–Meier Estimates of the Probability of Remaining Free of Primary Cardiovascular Events, According to Study Group.
The event rate for the primary cardiovascular end point at day 180 was 4.9% in the omeprazole group and 5.7% in the placebo group.

→ Among patients receiving aspirin and clopidogrel, prophylactic use of a PPI reduced the rate of upper gastrointestinal bleeding. There was no apparent cardiovascular interaction between clopidogrel and omeprazole, but our results do not rule out a clinically meaningful difference in cardiovascular events due to use of a PPI.

*D.L. Bhatt and Others | October 6, 2010 | (DOI: 10.1056/NEJMoa1007964)*
*http://www.nejm.org/doi/pdf/10.1056/NEJMoa1007964*

# Clopidogrel and Pharmacogenetic Test in Clinical Practice (one example)

- Vanderbilt University Medical Center joins Scripps Clinic, starting to routinely test for variations in *CYP2C19* gene before antiplatelet therapy

  Test for *1 (wild), 2, 3 (loss-of-function), 17 (gain-of-function)

  Individual clinicians to decide treatment options

  - If homozygous for loss-of-function
    → prasugrel
  - If contraindications for prasugrel
    → increase the dose from 75 to 150 mg
    or ticagrelor when it is available

http://www.theheart.org/article/1139495.do (October 21, 2010)

# Labeling Example (2)

## Warfarin

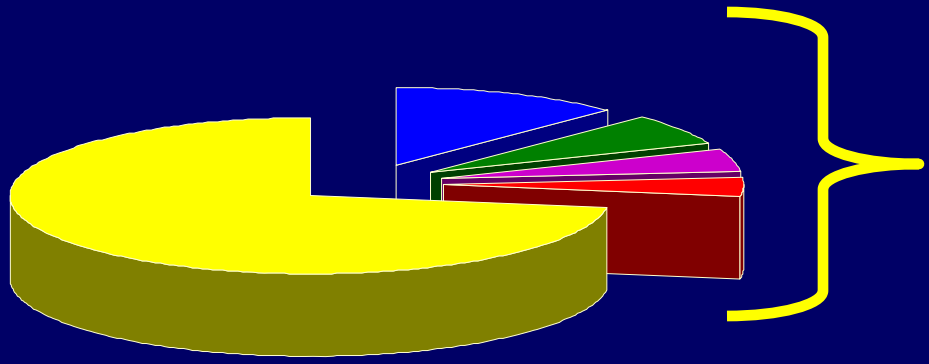
# Clinical Importance of Risk: Warfarin Eludes Patients Who Need It the Most

- Underutilization of warfarin and high rate of noncompliance due to physician and patient fear of bleeding
  - Prescribed to only 2/3 of appropriate candidates
- Other reasons for not starting warfarin treatment in A Fib patients (n = 300)
  - 28% prefer treatments without INR monitoring
  - 20% fear of bleeding
  - 18% would have difficulty to get INR monitored

*Choudhry et al, Br Med J, 2006, Patient Record Review on File at Astra-Zeneca, White et al, Am J Med 1999, Wolf, Arch Int Med 1987, Birman-Deych et al, Stroke 2006*

<Courtesy of Myong-Jin Kim, CDER presentation, September 2009>

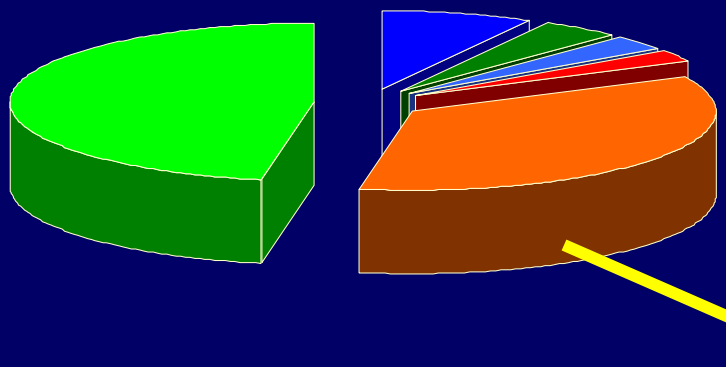
# Predicting the Warfarin Stable Dose



Age, Gender, Drugs,

BW, Race, Diet

Others



Genotypes (CYP2C9, VKORC1)

*Wadelius et al, Blood 2009, Gage et al, Clin Pharmacol Ther 2008, Caldwell et al, Clin Med Res 2007*

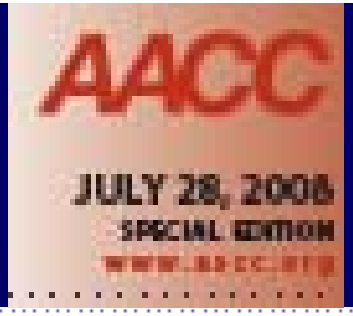
# Frequency of VKORC1

| -1639 G>A | AA | AG | GG |
|---|---|---|---|
| Caucasians (N=297) | 19% | 56% | 25% |
| Spanish (N=105) | 32% | 40% | 28% |
| Chinese (N=104) | 80% | 18% | 2% |
| African Americans (N=159) | 0% | 21% | 79% |

Asians may need a lower dose

<Sconce et al. Blood 2005, Yuan et al. Human Mol Genetics 2005, Schelleman et al. Clin Pharmacol Ther 2007, Montes et al Br J Haemat 2006>

# Public Debates




nature publishing group

PERSPECTIVES

See ARTICLE page 226

POINT/COUNTERPOINT

## The Critical Path of Warfarin Dosing: Finding an Optimal Dosing Strategy Using Pharmacogenetics

LJ Lesko[1]

## Warfarin and Pharmacogenomic Testing: The Case for Restraint

DA Garcia[1]

## Is Warfarin Pharmacogenomic Testing Ready for Prime Time?

*Today's Debate to Focus on Implementation Issues*



## Opponents Want More Data

*LJ Lesko, Clin Pharmacol & Ther, September 2008*
*DA Garcia, Clin Pharmacol & Ther, September 2008*

*AACC warfarin Debate: Hallworth, Huang, Eby, Linder, Jaffer, July 28, 2008http://www.aacc.org/publications/cln/2008/July/dailies/Pages/mon_daily1.aspx*

# January 2010 Relabeling

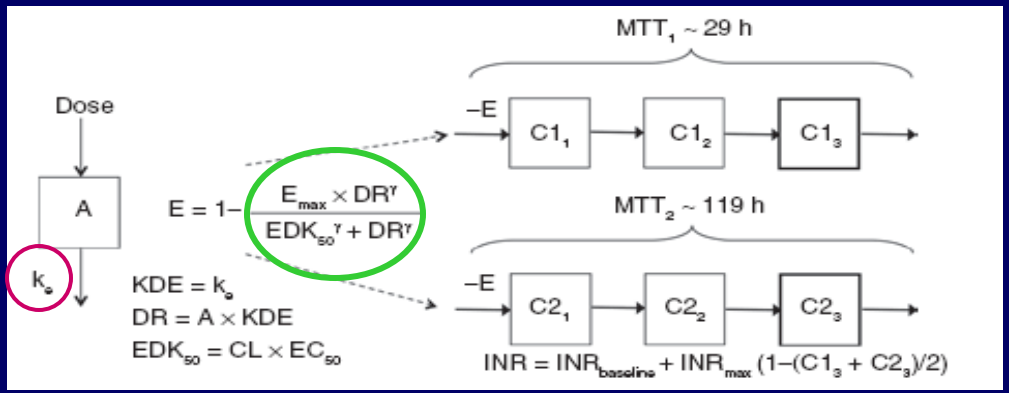
| VKORC1 ↓ | CYP2C9 *1*1 | CYP2C9 *1*2 | CYP2C9 *1*3 | CYP2C9 *2*2 | CYP2C9 *2*3 | CYP2C9 *3*3 |
|---|---|---|---|---|---|---|
| GG | 5-7 mg | 5-7 mg | 3-4 mg | 3-4 mg | 3-4 mg | .5-2 mg |
| AG | 5-7 mg | 3-4 mg | 3-4 mg | 3-4 mg | .5-2 mg | .5-2 mg |
| AA | 3-4 mg | 3-4 mg | .5-2 mg | .5-2 mg | .5-2 mg | .5-2 mg |

*Drugs at the FDA (COUMADIN, "Initial Dosage")*
*http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf*
*http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/*

# Predicted Warfarin Maintenace Dose

CYP2C9
*1/*1
*1/*2
*1/*3
*2/*2
*2/*3
*3/*3

CL=V*Ke




DR: drug-receptor

$EDK_{50}$ for VKOR1
G/G
G/A
A/A

**Table 4 Predicted maintenance doses of warfarin to achieve a target steady-state INR of 2.5 in typical 50-, 70-, and 90-year-old subjects with different combinations of *CYP2C9* and *VKORC1* genotypes to illustrate their relative influence on warfarin dose requirements**

| | *VKORC1* –1639 G>A (rs9923231) | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | G/G | | | G/A | | | A/A | | |
| *CYP2C9* | 50 years | 70 years | 90 years | 50 years | 70 years | 90 years | 50 years | 70 years | 90 years |
| *1/*1 | 8.5 | 7.6 | 6.7 | 6.2 | 5.6 | 4.9 | 4.0 | 3.6 | 3.2 |
| | (5.7–11.2) | (5.2–10.0) | (4.6–8.9) | (4.2–8.2) | (3.8–7.4) | (3.4–6.5) | (2.7–5.2) | (2.4–4.7) | (2.1–4.2) |
| *1/*2 | 6.4 | 5.7 | 5.1 | 4.7 | 4.2 | 3.7 | 3.0 | 2.7 | 2.4 |
| | (4.3–8.4) | (3.9–7.5) | (3.4–6.7) | (3.2–6.2) | (2.9–5.5) | (2.5–4.9) | (2.0–3.9) | (1.8–3.5) | (1.6–3.1) |
| *1/*3 | 5.3 | 4.7 | 4.2 | 3.9 | 3.5 | 3.1 | 2.5 | 2.2 | 2.0 |
| | (3.6–6.9) | (3.2–6.2) | (2.8–5.5) | (2.6–5.1) | (2.4–4.6) | (2.1–4.1) | (1.7–3.3) | (1.5–2.9) | (1.3–2.6) |
| *2/*2 | 4.3 | 3.8 | 3.4 | 3.1 | 2.8 | 2.5 | 2.0 | 1.8 | 1.6 |
| | (2.9–5.6) | (2.6–5.1) | (2.3–4.5) | (2.1–4.1) | (1.9–3.7) | (1.7–3.3) | (1.4–2.6) | (1.2–2.4) | (1.1–2.1) |
| *2/*3 | 3.2 | 2.8 | 2.5 | 2.3 | 2.1 | 1.8 | 1.5 | 1.3 | 1.2 |
| | (2.1–4.2) | (1.9–3.7) | (1.7–3.3) | (1.6–3.1) | (1.4–2.8) | (1.3–2.4) | (1.0–2.0) | (0.9–1.8) | (0.8–1.6) |
| *3/*3 | 2.1 | 1.8 | 1.6 | 1.5 | 1.4 | 1.2 | 1.0 | 0.9 | 0.8 |
| | (1.4–2.7) | (1.3–2.4) | (1.1–2.2) | (1.0–2.0) | (0.9–1.8) | (0.8–1.6) | (0.7–1.3) | (0.6–1.1) | (0.5–1.0) |

Values within parentheses represent corresponding doses for a target steady-state INR of 2.0 and 3.0, respectively.
INR, international normalized ratio.

*<Hamberg et al, Clin Pharmacol Ther, 2010>*

# Warfarin Drug Interactions -Jan 2010 Labeling

| Specific Drugs Reported | | |
|---|---|---|
| acetaminophen | fenofibrate | oxymetholone |
| alcohol† | fenoprofen | pantoprazole |
| allopurinol | fluconazole | paroxetine |
| aminosalicylic acid | fluorouracil | penicillin G, intravenous |
| amiodarone HCl | fluoxetine | pentoxifylline |
| argatroban | flutamide | phenylbutazone |
| aspirin | fluvastatin | phenytoin† |
| atenolol | fluvoxamine | piperacillin |
| atorvastatin† | gefitinib | piroxicam |
| azithromycin | gemfibrozil | pravastatin† |
| bivalirudin | glucagon | prednisone† |
| capecitabine | halothane | propafenone |
| cefamandole | heparin | propoxyphene |
| cefazolin | ibuprofen | propranolol |
| cefoperazone | ifosfamide | propylthiouracil† |
| cefotetan | indomethacin | quinidine |
| cefoxitin | influenza virus vaccine | quinine |
| ceftriaxone | itraconazole | rabeprazole |
| celecoxib | ketoprofen | ranitidine† |
| cerivastatin | ketorolac | rofecoxib |
| chenodiol | lansoprazole | sertraline |
| chloramphenicol | lepirudin | simvastatin |
| chloral hydrate† | levamisole | stanozolol |
| chlorpropamide | levofloxacin | streptokinase |
| cholestyramine† | levothyroxine | sulfamethizole |
| cimetidine | liothyronine | sulfamethoxazole |
| ciprofloxacin | lovastatin | sulfinpyrazone |
| cisapride | mefenamic acid | sulfisoxazole |
| clarithromycin | methimazole† | sulindac |
| clofibrate | methyldopa | tamoxifen |
| COUMADIN overdose | methylphenidate | tetracycline |
| cyclophosphamide† | methylsalicylate ointment (topical) | thyroid |
| danazol | metronidazole | ticarcillin |
| dextran | miconazole (intravaginal, oral, systemic) | ticlopidine |
| dextrothyroxine | moricizine hydrochloride† | tissue plasminogen activator (t-PA) |
| diazoxide | nalidixic acid | tolbutamide |
| diclofenac | naproxen | tramadol |
| dicumarol | neomycin | trimethoprim/sulfamethoxazole |
| diflunisal | norfloxacin | urokinase |
| disulfiram | ofloxacin | valdecoxib |
| doxycycline | olsalazine | valproate |
| erythromycin | omeprazole | vitamin E |
| esomeprazole | oxandrolone | zafirlukast |
| ethacrynic acid | oxaprozin | zileuton |
| ezetimibe | | |

also; other medications affecting blood elements which may modify hemostasis

http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/009218s108lbl.pdf

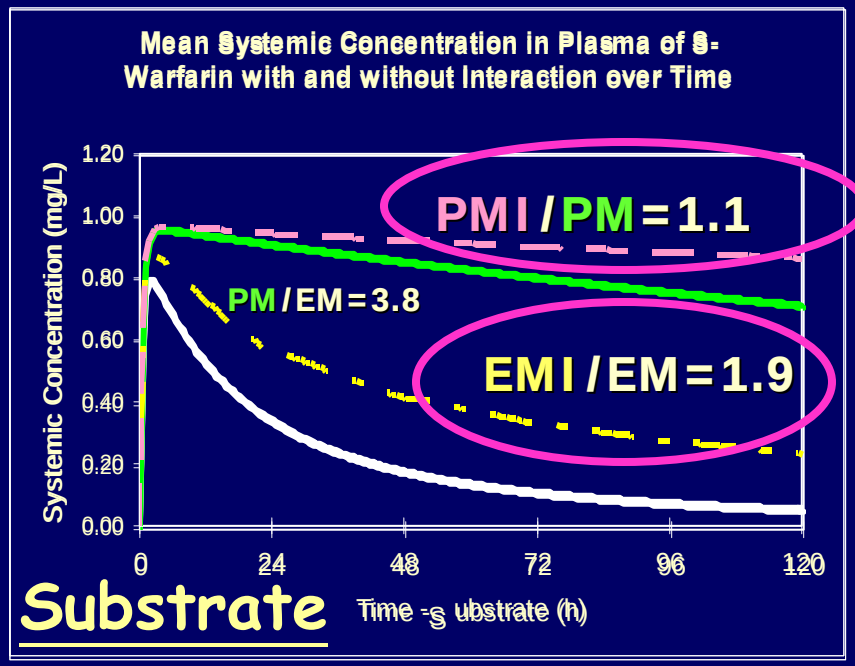
# Genotype- Specific Inhibition Effect

**Pop 1: CYP2C9 EM; Pop 2: CYP2C9 PM, M/F=1.0; Age 20-40 yr**
***S-warfarin: SD 10 mg on day 1***
***Sulfaphenazole: QD 2000 mg 5 days***

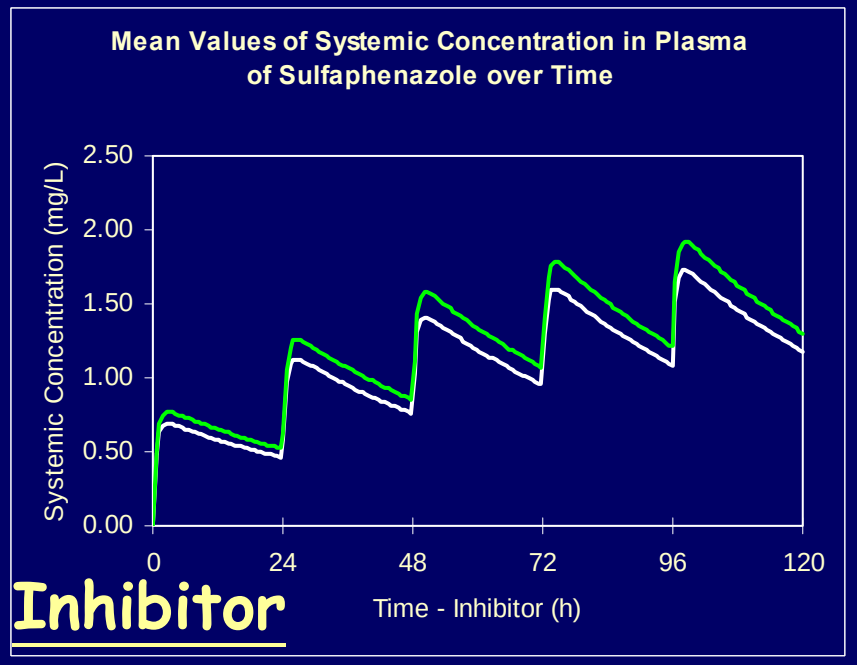
| 7-OH Warfarin | EM (*1/*1) | PM (*3/*3) |
|---|---|---|
| $CL'_{int}$ (uL/min/pmol CYP) | 0.034 | 0.005 |

***Using SimCYP® V8.20***

___ EM Control
___ PM Control
_ _ _ EM +Inh.
_ _ _ PM +Inh.




___ EM Control
___ PM Control

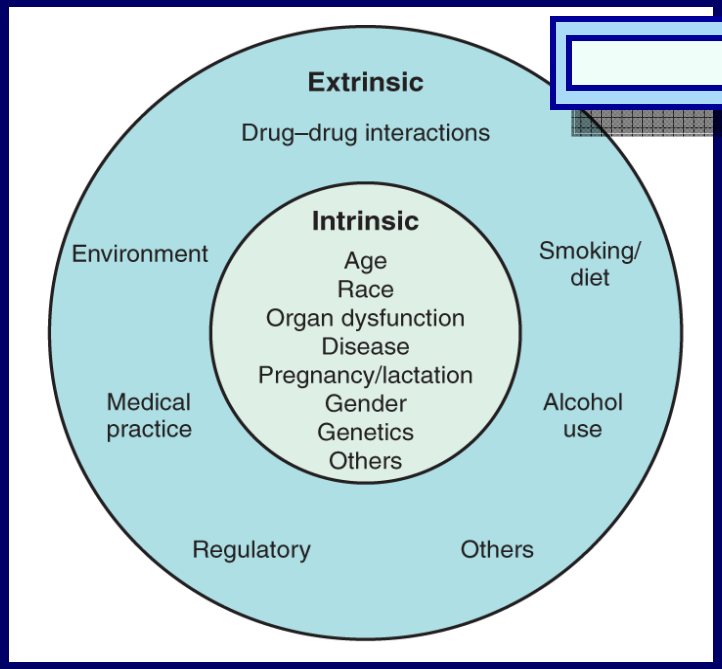



‹Zhao P, Zhang L, Lesko L, Huang S-M, LOL presentation, Merrimac, WI, September 2009›

→ Which population needs dose adjustment? (e.g., atmoxetine labeling)

# PBPK: Application of PBPK in Clinical Pharmacology Evaluation

## A. Intrinsic/extrinsic Factors



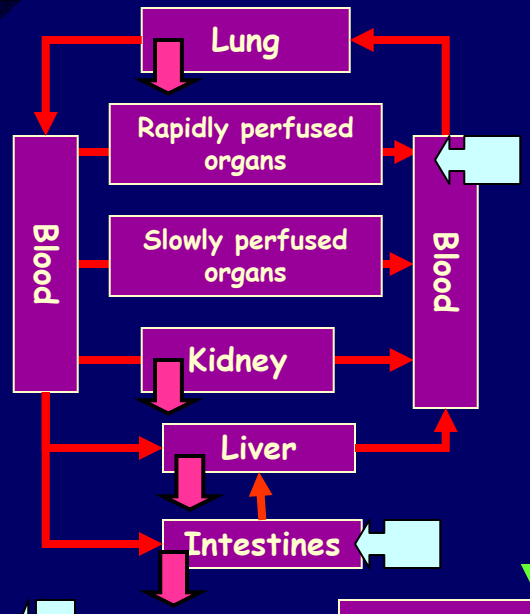

*Huang and Temple, 2008*

Individual or combined effects on human physiology

## B. PBPK Model components

System component (drug-independent)

Drug-dependent component




Dosing

Elimination

ADME, PK, PD and MOA

*Metabolism*
*Active transport*
*Passive diffusion*
*Protein binding*
*Drug-drug interactions*
*Receptor binding*

PBPK Model

Predict, Learn, Confirm

*<Zhao P, et al, Clin Pharmacol Ther, in press>*

# Labeling Example (3)

Statins
&
Transporters

# Drugs Withdrawn from the US Market due to Safety Reasons

| Withdrawn | Approv | Drug name | Use | Risk |
|---|---|---|---|---|
| 1998 | 1997 | Mibefradil | High blood pressure/Chronic stable angina | Torsades de Pointes; Drug-drug interactions; |
| 1998 | 1997 | Bromfenac | NSAID | Acute liver failure |
| 1998 | 1985 | Terfenadine | Antihistamine | Torsades de Pointes; Drug-drug interactions |
| 1999 | 1988 | Astemizole | Antihistamine | Torsades de Pointes; Drug-drug interactions |
| 1999 | 1997 | Grepafloxacin | Antibiotics | Torsades de Pointes |
| 2000(2002)* | 2000 | Alosetron* | Irritabl bowel syndrome in women | Ischemic colitis; complications of constipation |
| 2000 | 1993 | Cisapride | Heartbu | Torsades de Pointes; Drug-drug interactions |
| 2000 | 1997 | Troglitazone | Diabetes | Acute liver failure |
| 2001 | 1997 | Cerivastatin | Cholesterol low ng | Rhabdomyolysis; Drug-drug interactions |
| 2001 | 1999 | Rapacuronium | Anesthesia | Bronchospasm |
| 2003 | 1993 | Levomethadyl | Opiate dependence | Fatal arrhythmia |
| 2004 | 1999 | Rofexocib | Pain relief | |
| 2005 | 2001 | Valdecoxib | Pain relief | Skin reactions (SJS) |
| 2005(2006)* | 2004 | Natalizumab* | Multiple sclerosis | Brain infection |
| 2005 | 2004 | 99m Tc** | Diagnostic aid | Cardiopulmonary arrest |
| 2005 | 1975 | Pemoline | ADHD | Liver failure |

CYP/transporter inhibitor

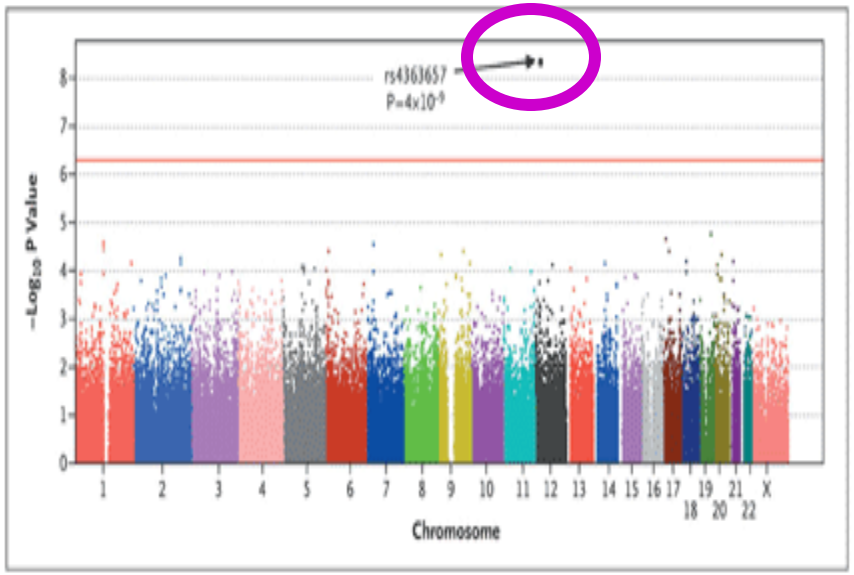
CYP/transporter substrate

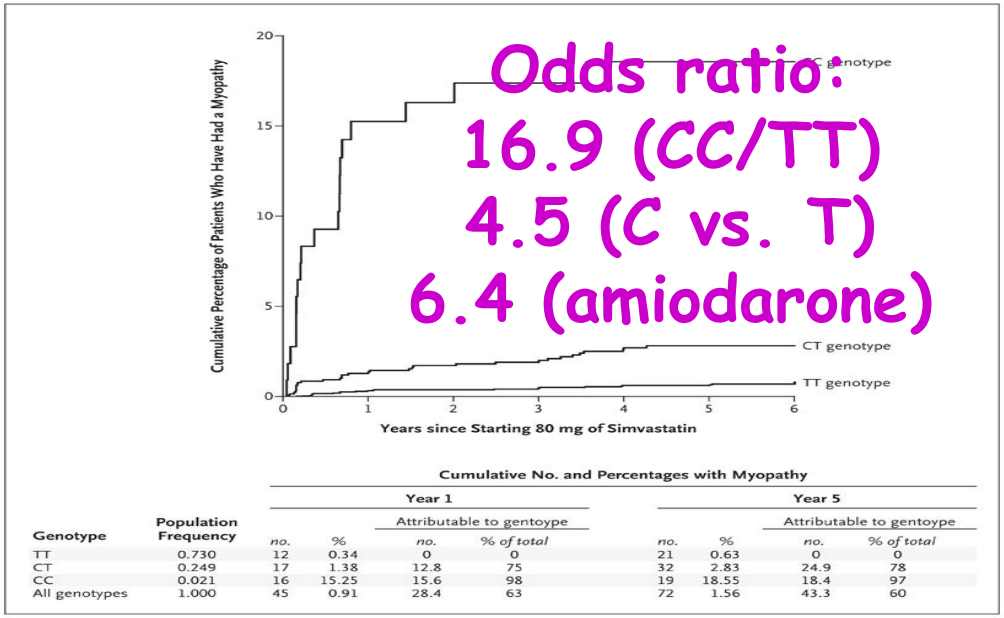
* remarketed with restricted distribution ** Technetium (99m Tc) fanolesomab

*Huang, S-M, et al, "Principles of Gender-Specific Medicine", Ed., Legato M, Academic Press, 2004, pp 848-859 ; Huang, S-M, et al, Toxicology Mechanisms and Methods, 16: 89-99, 2006*

# Pharmacogenetics (simvastatin) -Myopathy-

## Genomewide Association



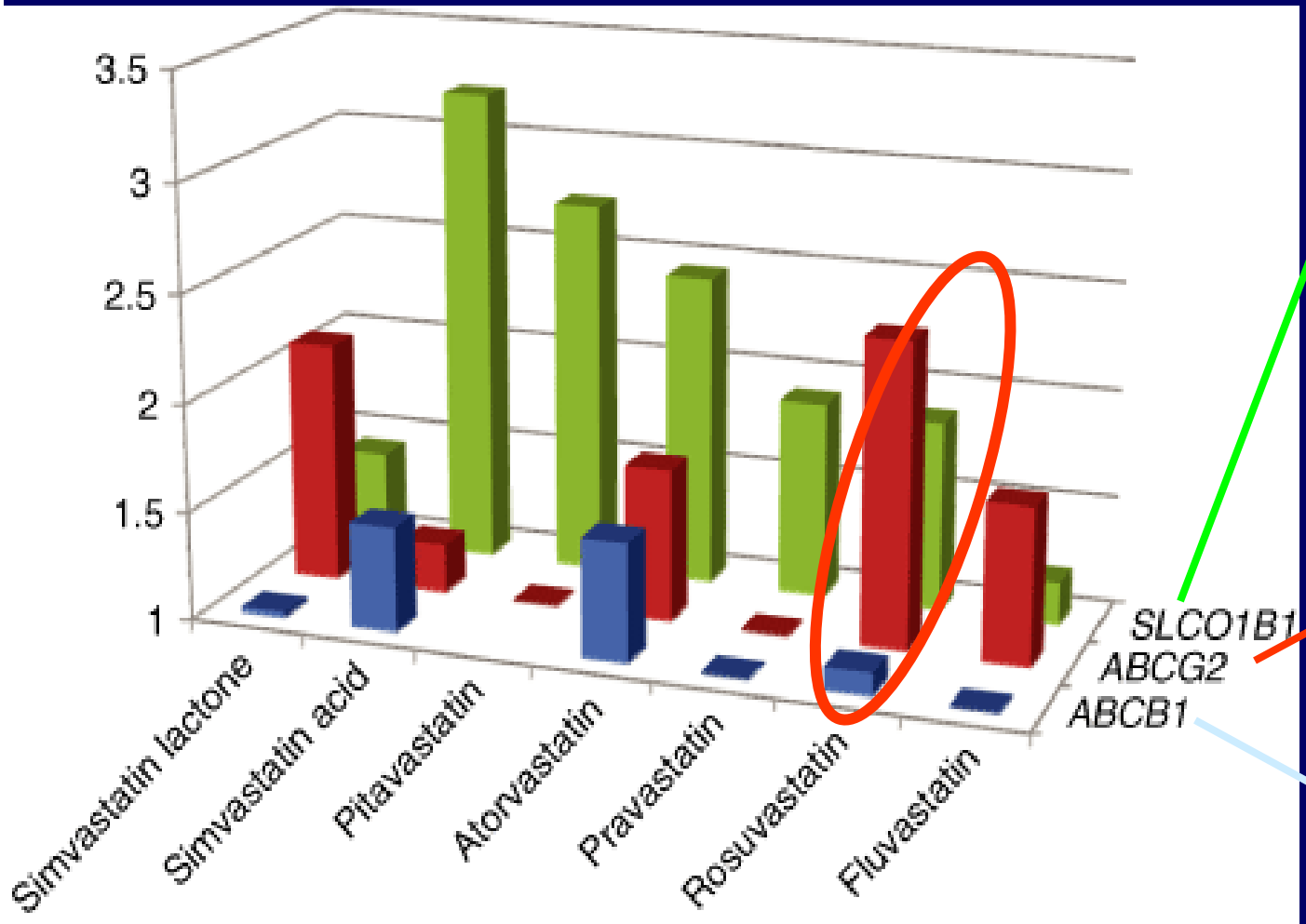

Cumulative No. and Percentages with Myopathy

| Genotype | Population Frequency | Year 1 | | Year 1 Attributable to gentoype | | Year 5 | | Year 5 Attributable to gentoype | |
|---|---|---|---|---|---|---|---|---|---|
| | | no. | % | no. | % of total | no. | % | no. | % of total |
| TT | 0.730 | 12 | 0.34 | 0 | 0 | 21 | 0.63 | 0 | 0 |
| CT | 0.249 | 17 | 1.38 | 12.8 | 75 | 32 | 2.83 | 24.9 | 78 |
| CC | 0.021 | 16 | 15.25 | 15.6 | 98 | 19 | 18.55 | 18.4 | 97 |
| All genotypes | 1.000 | 45 | 0.91 | 28.4 | 63 | 72 | 1.56 | 43.3 | 60 |

1. Estimated Cumulative Risk of Myopathy Associated with Taking 80 mg of Simvastatin Daily, according to SLCO1B1 rs4149056 Genotype (c.521T>C)
2. Association replicated in another 40 mg group

*The SEARCH Collaborative Group. N Engl J Med 2008; 359: 789-799 (UK)*

# Fold-Change in Plasma AUC
# - Effect of Transporter Genetics -




(OATP1B1)
c.521CC/TT

c.521T>C
White: Black: Asian
15-20: 2 : 10-15%

(BCRP)
c.421AA/CC

c.421 C>A
White: Black: Asian
15-20: 0-5 : 25-35%

(P-gp)
c.1236TT/CC
c.2677TT/GG
c.3435TT/CC

*Data from Niemi M, Clin Pharmacol Ther 87:130, January 2010*

# OATP1B1

"Eltrombopag is an inhibitor of OATP1B1 transporter. Monitor patients closely for signs and symptoms of excessive exposure to the drugs that are substrates of OATP1B1 (e.g., rosuvastatin) and consider reduction of the dose of these drugs."

The following were listed as OATP1B1 substrates: "benzylpenicillin, atorvastatin, fluvastatin, pravastatin, rosuvastatin, methotrexate, nateglinide, repaglinide, rifampin"

*Drugs at the FDA (Promacta,November 2008, "Highlights" and "Drug Interactions")*
*http://www.accessdata.fda.gov/scripts/cder/drugsatfda/index.cfm?fuseaction=Search.Label_ApprovalHistory*
http://www.accessdata.fda.gov/Scripts/cder/DrugsatFDA/

# Labeling of Simvastatin

## TABLE 1 Drug Interactions Associated with Increased Risk of Myopathy/Rhabdomyolysis

- Itraconazole Ketoconazole Erythromycin Clarithromycin Telithromycin HIV protease inhibitors Nefazodone

→Avoid simvastatin

- Gemfibrozil Cyclosporine Danazol

→ Do not exceed 10 mg simvastatin daily

- Amiodarone Verapamil

→ Do not exceed 20 mg simvastatin daily

- Diltiazem

→ Do not exceed 40 mg simvastatin daily

Chinese Patients Taking Lipid-Modifying Doses (≥1 g/day Niacin) of Niacin-containing Products

→Do not take 80 mg

- Grapefruit juice

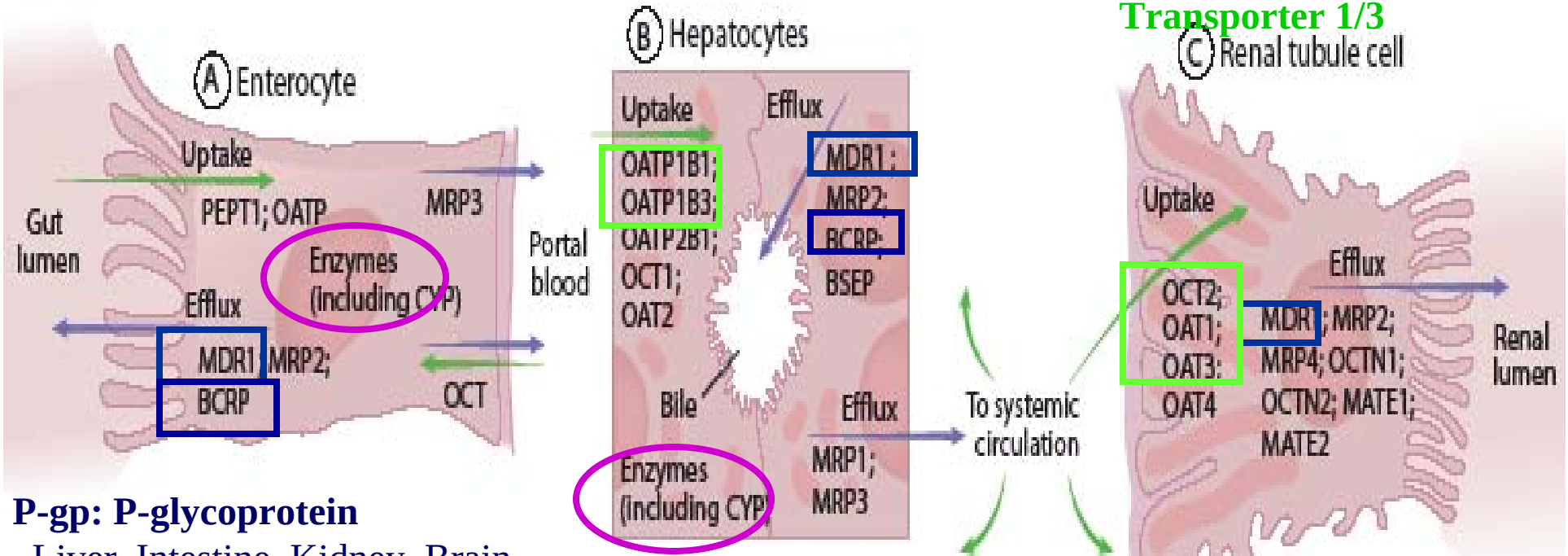
→ Avoid large quantities of grapefruit juice (>1 quart daily)

*Simvastatin labeling (Zocor), April 2010:*
*http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/019766s080lbl.pdf*

# Selected efflux & uptake transporters in the gut wall (a), liver (b), and kidneys (c)

- **OCT2: Organic Cation Transporter 2**
- **OAT1/3: Organic Anion Transporter 1/3**

**OATP: Organic Anion Transporting Polypeptide**




**P-gp: P-glycoprotein**

Liver, Intestine, Kidney, Brain

**BCRP: Breast Cancer Resistant Protein**

Liver, Intestine, Kidney, Brain

Huang S-M, Lesko LJ, and Temple R, "Adverse Drug Reactions and Pharmacokinetic Drug Interactions", Chapter 21, Adverse Drug Reactions and Drug Interactions in Part 4, FUNDAMENTAL PRINCIPLES: Clinical Pharmacology, "Pharmacology and Therapeutics: Principles to Practice," Ed. Waldman & Terzic, Elsevier, 2009

DIA Drug Information Association FDA

# FDA Critical Path Transporter Workshop

in collaboration with PhRMA aaps American Association of Pharmaceutical Scientists ISSX

October 2-3, 2008 | Marriott Bethesda North Hotel & Conference Center, Bethesda MD, USA

# White Paper

## From the "International Transporter Consortium"

1. Overview of Transporters

   Overview, MDR1, BCRP, OAT/OCT, OATP

2. Methods for Studying Transporters

   Cell/membrane models, intact organ/in vivo models; modeling/imaging tools, enzyme/transporter interplay

3. Drug Development Issues

   Overview/example cases; decision trees


1. *International Transporter Consortium, Nature Reviews Drug Discovery, March 2010*
2. *Huang S-M, Woodcock J, Nature Reviews Drug Discovery, March 2010*
3. *Huang S-M, Zhang L, Giacomini, Clin Pharmacol Ther, Jan 2010*


→Follow up workshop in March 2012 in Bethesda/Washington DC area

# Summary

- Individual variations in drug response may be attributed to various intrinsic and extrinsic factors; genetics is one of the factors and needs to be considered along with other factors
- It is important to assess safety, effectiveness and dose-exposure response in various subgroups during drug development and apply the results of exposure-response to better define optimum individual dosing regimens

# Summary (2)

- As the pharmacogenetics/ pharmacogenomics information becomes available, its association with the safe and effective use of drugs has been incorporated in the drug label and some tests have been incorporated into clinical practice
- Challenges need to be continued to be addressed in the translation of genetic information to product labeling and clinical practice

# Summary (3)

- Collaboration is key to future successes
- Application of modeling/simulation (e.g., PBPK) is critical to optimal study design and to addressing issues related to multiple inhibitors/multiple patient factors
- Various guidance documents in development will discuss premarketing evaluation of pharmacogenetics in early phase clinical studies, drug interactions, others

FDA OTS dashboard:
http://www.fda.gov/AboutFDA/WhatWeDo/track/ucm206444.htm#progmeas

# References

FDA Drug Development and Drug Interactions Website;
*http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm080499.htm*

Genomics at the FDA:
*http://www.fda.gov/Drugs/ScienceResearch/ResearchAreas/Pharmacogenetics/default.htm*

Drugs@FDA;
*http://www.accessdata.fda.gov/scripts/cder/drugsatfda/*

Clinical Pharmacology Guidance for industry:
*http://www.fda.gov/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm064982.htm*

For Consumers:
*http://www.fda.gov/ForConsumers/ConsumerUpdates/ucm212747.htm*